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Synthesis of trisubstituted isoxazoles via in situ trapping strategy from α-nitro carbonyl compounds and methyl ketones or terminal aryl alkenes

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ABSTRACT

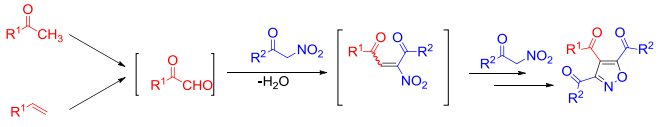
A highly efficient domino method for the synthesis of trisubstituted isoxazoles has been established from α-nitro carbonyl compounds and methyl ketones or terminal aryl alkenes. Simple and readily available starting materials, mild reaction conditions and very simple operation are significant advantages of the reaction.

1. Introduction

The in situ trapping of unstable intermediates via domino reactions has provided enormous opportunities for the efficient synthesis of complex products from simple substrates.[1] Recently, we have successfully developed several novel domino reactions for the synthesis of 1,4-enediones via in situ trapping of unstable α-ketoaldehyde intermediates.[2] To further expand this strategy for the synthesis of pharmacologically interesting heterocycles, we report herein a new and efficient domino method for the synthesis of trisubstituted isoxazoles.

Isoxazoles have long been attractive targets for synthetic chemists due to their well known biological activities, such as antibacterial,[3] antiviral,[3] anticancer,[4] and antithrombotic activity.[5] In addition, they also serve as versatile building blocks in organic synthesis[6] and materials science.[7] Consequently, a variety of methods have been developed for their synthesis, such as condensation of hydroxylamine with 1,3-dicarbonyl compounds,[8] cyclization of propargylic oximes,[9] rearrangement of subsituted oxetanes,[10] reaction of nitroacetates with dipolarophiles,[11] 1,3-dipolar cycloaddition of nitrile oxides with alkynes,[12] and multicomponent reactions.[13] However, many of these methods suffer from narrow substrate scopes and modest regioselectivities. Thus, a general and regioselective method is still highly needed for chemists to construct isoxazoles from simple and readily available starting materials.

In our previous studies,[2] methyl ketones or terminal aryl alkenes could be in situ transformed to α-ketoaldehydes via domino iodination–Kornblum oxidation reaction. Correspondingly, we suppose that α-nitro carbonyl compounds with acidic methylenes could in situ trap the unstable α-ketoaldehyde intermediates via Knoevenagel-type condensation to generate 2-nitro-1,4-enediones, which may further react with α-nitro carbonyl compounds to regioselectively afford trisubstituted isoxazoles due to the activating and leaving ability of nitro group (Scheme 1).[11d]



Scheme 1. Proposed reaction pathway.

2. Results and discussion

To verify our hypothesis, the initial study started with the reaction between acetophenone **1a** and ethyl nitroacetate **3a**. Fortunately, treatment of **1a** with **3a** in the presence of 1.0 equiv of CuO and 1.0 equiv of I_2 in DMSO at 70 °C furnished the desired isoxazole **4aa** in 72% yield (Table 1, Entry 1), which was unambiguously confirmed by X-ray diffraction (Fig. 1).[14] Much to our satisfaction, by increasing the CuO and I_2 loading to 2.0 equiv, isoxazole **4aa** was

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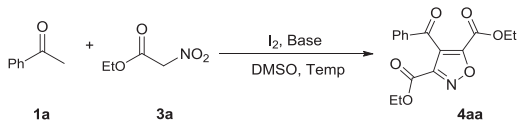
obtained in 85% yield after 16 h (Table 1, entry 4). However, further increase the temperature led to lower yields, possibly due to the overoxidation of α-ketoaldehyde intermediates at high temperature.[2] On the other hand, other bases employed under this condition failed to give the desired products (Table 1, entries 7–10).

Table 1
Optimization of the reaction conditions[a]



Entry	Base (equiv)	I_2 (equiv)	*t* (h)	Temp (°C)	Yield (%)[b]
1	CuO (1.0)	1.0	24	70	72
2	CuO (2.0)	1.0	24	70	74
3	CuO (1.0)	2.0	24	70	70
4	CuO (2.0)	2.0	16	70	85
5	CuO (2.0)	2.0	16	80	62
6	CuO (2.0)	2.0	16	90	51
7	K_2CO_3 (2.0)	2.0	24	70	—[c]
8	Et_3N (2.0)	2.0	24	70	—[c]
9	DABCO (2.0)	2.0	24	70	—[c]
10	DBU (2.0)	2.0	24	70	—[c]

[a] Reaction conditions: **1a** (1.0 mmol), **3a** (2.0 mmol) in 5 mL of DMSO under an atmosphere of argon.
[b] Isolated yields.
[c] No desired product was obtained.

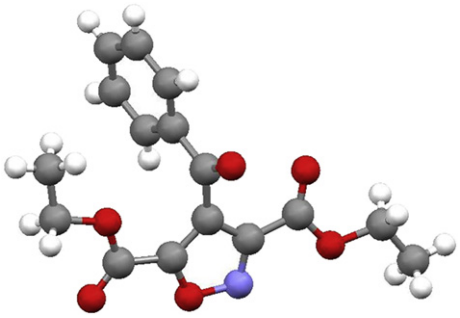
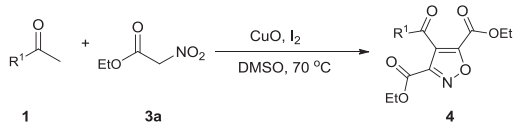


Fig. 1. X-ray structure of compound **4aa**.

With the optimized result in hand, we first explored the scope of methyl ketones for this reaction (Table 2). Pleasingly, electron neutral (H, CH_3), electron-donating (OCH_3) and sterically hindered (1-naphthyl, 2-naphthyl) methyl ketones all reacted efficiently to give the desired isoxazoles in good to excellent excellent yields (78–85%; entries 1–3 and 5–6). However, when strong electron-withdrawing group (−NO_2) was attached to the phenyl ring of methyl ketone, the yield dropped substantially (55%; entry 4). To our delight, good yields were also obtained for halogenated (−Cl, −Br, −F) methyl ketones (71–77%; entries 7–9). Much to our satisfaction, furanyl, benzofuranyl, and thienyl methyl ketones could also give the corresponding isoxazoles in moderate yields (62–67%; entries 10–12). It's noteworthy that α,β-unsaturated methyl ketones with various substituents could also give the corresponding isoxazoles in moderate to good yields (54–69%; entries 13–16).

According to our previous studies,[2d,e] the substrates were next extended to terminal aryl alkenes, which could also be in situ transformed to α-ketoaldehydes (Table 3). Fortunately, electron neutral (H, CH_3), electron-donating (OCH_3), sterically hindered (2-naphthyl), and halogenated (−Cl, −Br, −F) terminal aryl alkenes were all compatible under this condition, and generally moderate to good yields were obtained (62–78%).

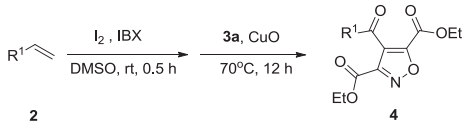
Table 2
Scope of methyl ketones[a]



Entry	1	4	Yield (%)[b]
1	**1a** (C_6H_4)	**4aa**	85
2	**1b** (4-MeC_6H_4)	**4ba**	83
3	**1c** (4-$MeOC_6H_4$)	**4ca**	78
4	**1d** (4-$NO_2C_6H_4$)	**4da**	55
5	**1e** (1-Naphthyl)	**4ea**	79
6	**1f** (2-Naphthyl)	**4fa**	82
7	**1g** (4-ClC_6H_4)	**4ga**	74
8	**1h** (4-BrC_6H_4)	**4ha**	77
9	**1i** (4-FC_6H_4)	**4ia**	71
10	**1j** (2-Thienyl)	**4ja**	67
11	**1k** (2-Furyl)	**4ka**	62
12	**1l** (2-Benzofuryl)	**4la**	65
13	**1m** ((*E*)-Ph−CH=CH−)	**4ma**	69
14	**1n** ((*E*)-4-$MeOC_6H_5$−CH=CH−)	**4na**	61
15	**1o** ((*E*)-4-$NO_2C_6H_5$−CH=CH−)	**4oa**	54
16	**1p** ((*E*, *E*)-C_6H_5−$(CH=CH)_2$−)	**4pa**	57

[a] Reaction conditions: **1** (1.0 mmol), **3a** (2.0 mmol), CuO (2.0 mmol), and I_2 (2.0 mmol) in DMSO (5 mL) for 16 h at 70 °C under an atmosphere of argon.
[b] Isolated yields.

Table 3
Scope of terminal aryl alkenes[a]



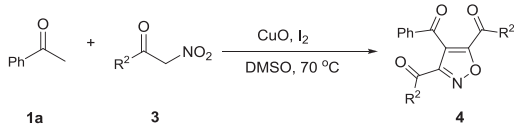
Entry	2	4	Yield (%)[b]
1	**2a** (C_6H_5)	**4aa**	78
2	**2b** (4-MeC_6H_4)	**4ba**	76
3	**2c** (4-$MeOC_6H_4$)	**4ca**	71
4	**2d** (2-naphthyl)	**4fa**	62
5	**2e** (4-ClC_6H_4)	**4ga**	67
6	**2f** (4-BrC_6H_4)	**4ha**	66
7	**2g** (4-FC_6H_4)	**4ia**	62

[a] Reaction was performed with terminal aryl alkene **2** (1.0 mmol), IBX (1.2 mmol), and I_2 (2.0 mmol) in DMSO (5 mL) at room temperature for 0.5 h, then **3a** (2.0 mmol) and CuO (2.0 mmol) were added, and the mixture was stirred at 70 °C for 12 h.
[b] Isolated yield.

Using acetophenone, structural variations in the α-nitromethyl ketones were then examined (Table 4). Although a moderate yield was obtained for aliphatic α-nitroketone (44%, entry 1), good yields (75–85%; entries 2–7) were obtained for aryl α-nitroketones with electron−neutral (−H, −Me), electron-rich (−OMe), electron-deficient (−NO_2) and halogen substituents (−Cl, −Br, −F). Fortunately, the structure of **4ab** was also confirmed by X-ray diffraction (Fig. 2).[14]

Based on these results, a possible reaction mechanism is shown as follows (Scheme 2) using acetophenone **1a**, styrene **2a**, and ethyl nitroacetate **3a** as an example: acetophenone **1a** or styrene **2a** could be in situ transformed to phenylglyoxal **B** via domino iodination–Kornblum oxidation reaction, which could further undergo Knoevenagel-type condensation with ethyl nitroacetate **3a** to generate 2-nitro-1,4-enedione intermediate **C**. Further Michael addition of **3a** to intermediate **C** afforded intermediate **D**, which could undergo intramolecular nucleophilic *O*-alkylation to give isoxazoline *N*-oxide intermediate **E**. Isomerization of intermediate **E** led to *N*-hydroxy intermediate **F**, which was finally converted into isoxazole **4aa** by elimination of a molecule of water.

Table 4
Scope of α-nitroketones[a]



1a 3 4

Entry	3 (R^2)	4	Yield (%)[b]
1	**3b** (*i*-Pr)	**4ab**	44
2	**3c** (Ph)	**4ac**	85
3	**3d** (4-MeC_6H_4)	**4ad**	83
4	**3e** (4-$MeOC_6H_4$)	**4ae**	79
5	**3f** (4-$NO_2C_6H_4$)	**4af**	81
6	**3g** (4-ClC_6H_4)	**4ag**	79
7	**3h** (4-BrC_6H_4)	**4ah**	75

[a] Reaction conditions: **1a** (1.0 mmol), **3** (2.0 mmol), CuO (2.0 mmol), and I_2 (2.0 mmol) in DMSO (5 mL) for 16 h at 70 °C under an atmosphere of argon.
[b] Isolated yields.

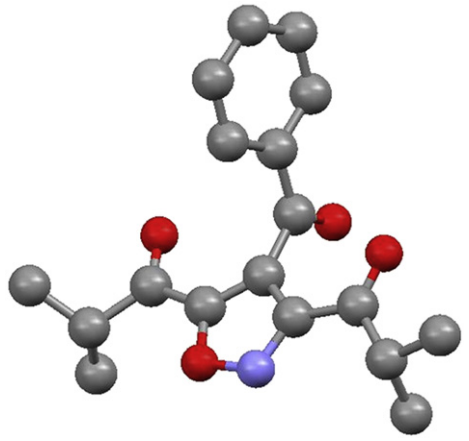
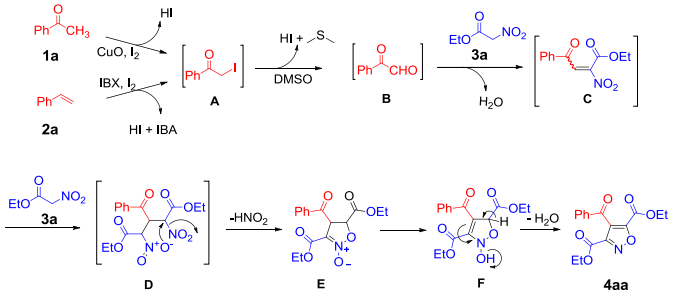


Fig. 2. X-ray structure of compound **4ab** (all hydrogen atoms are omitted for clarity).



Scheme 2. Proposed reaction mechanism.

3. Conclusion

In conclusion, we have developed an efficient route for the synthesis of isoxazoles from easily available α-nitroketones and methyl ketones or terminal aryl alkenes. This method not only represents an interesting domino process but also provides a practical access to trisubstituted isoxazoles with potential applications in the drug discovery.

4. Experimental section

4.1. General methods

All commercially available reagents were used without further purification. α-Nitroketones **3b**–**3h** were prepared according to the literature method.[15] Reactions were carried out under an argon atmosphere unless indicated otherwise. Solvents were dried according to published methods and distilled before use. IR spectra were recorded on an infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H spectra were recorded in $CDCl_3$ on 400/600 MHz NMR spectrometers. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet), coupling constants (Hz) and integration. ^{13}C spectra were recorded in $CDCl_3$ on 100/150 MHz spectrometers and resonances (δ) are given in parts per million relative to the center line of a triplet at 77.0 ppm of chloroform-*d*. HRMS were obtained on a FT-ICR MS equipped with an electrospray source. Column chromatography was performed on silica gel (200–300 mesh).

4.2. General procedure for the preparation of isoxazoles 4 from methyl ketones 1 and α-nitro carbonyl compounds 3

Methyl ketone **1** (1.0 mmol), α-nitro carbonyl compound **3** (2.0 mmol), CuO (2.0 mmol), and iodine (2.0 mmol) were placed in an oven-dried and argon filled Schlenk tube. After addition of anhydrous DMSO (5 mL), the mixture was stirred at 70 °C for 16 h. After the reaction completed (monitored by TLC), the reaction mixture was cooled to room temperature, then filtered through a layer of silica gel and eluted with EtOAc. The filtrate was diluted with water and treated with $Na_2S_2O_3$ (5% w/w, aq) until the color turned to pale yellow. The mixture was then extracted with additional EtOAc (2×30 mL), the combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation, the crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the pure product **4**.

4.3. General procedure for the preparation of isoxazoles 4 from α-nitro carbonyl compounds 3 and terminal aryl alkenes 2

To an oven-dried and argon filled Schlenk tube was added IBX (1.2 mmol) and anhydrous DMSO (5 mL), followed by terminal aryl alkene **2** (1.0 mmol) and iodine (2.0 mmol). The reaction mixture was stirred at room temperature for 0.5 h, then ethyl nitroacetate **3a** (2.0 mmol) and CuO (2.0 mmol) were added, the mixture was stirred at 70 °C for 12 h. After the reaction completed (monitored by TLC), the reaction mixture was cooled to room temperature, then filtered through a layer of silica gel and eluted with EtOAc. The filtrate was diluted with water and treated with $Na_2S_2O_3$ (5% w/w, aq) until the color turned to pale yellow. The mixture was then extracted with additional EtOAc (2×30 mL), the combined organic layers were washed with NaOH (5% w/w, aq) and brine successively. After drying over Na_2SO_4 and evaporation, the crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the product **4**.

4.4. Spectroscopic data

*4.4.1. Diethyl 4-benzoylisoxazole-3,5-dicarboxylate (**4aa**).* White solid; mp 109–110 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.83 (d, *J*=7.2 Hz, 2H), 7.64 (t, *J*=7.2 Hz, 1H), 7.50 (t, *J*=7.2 Hz, 2H), 4.33–4.25 (m, 4H), 1.20 (t, *J*=7.2 Hz, 3H), 1.12 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 186.2, 158.5, 157.9, 155.1, 155.0, 136.1, 134.3, 129.2, 128.8, 123.4, 63.0, 62.9, 13.6, 13.4; IR (KBr): 1746, 1682, 1277, 1239, 1029, 849 cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{16}H_{15}NNaO_6$: 340.0791; found: 340.0788.

*4.4.2. Diethyl 4-(4-methylbenzoyl)isoxazole-3,5-dicarboxylate (**4ba**).* White solid; mp 82–83 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.71 (d, *J*=7.8 Hz, 2H), 7.29 (d, *J*=7.8 Hz, 2H), 4.33–4.26 (m, 4H), 2.44 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H), 1.14 (t, *J*=7.2 Hz, 3H); ^{13}C

NMR ($CDCl_3$, 100 MHz): δ (ppm) 185.8, 158.3, 157.8, 155.1, 154.9, 145.5, 133.6, 129.5, 129.3, 123.5, 62.9, 62.8, 21.8, 13.6, 13.5; IR (KBr): 1749, 1680, 1602, 1309, 1275, 1226, 1181, 1024, 915, 837 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_6$: 332.1129; found: 332.1127.

*4.4.3. Diethyl 4-(4-methoxybenzoyl)isoxazole-3,5-dicarboxylate (**4ca**).* White solid; mp 86–88 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.79 (d, *J*=8.4 Hz, 2H), 6.96 (d, *J*=8.4 Hz, 2H), 4.34–4.27 (m, 4H), 3.89 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H), 1.15 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 184.6, 164.5, 158.3, 157.9, 155.2, 155.0, 131.6, 129.4, 123.6, 114.1, 62.93, 62.87, 55.6, 13.7, 13.6; IR (KBr): 1750, 1669, 1600, 1262, 1226, 1179, 1026, 914, 845 cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{17}NNaO_7$: 370.0897; found: 370.0897.

*4.4.4. Diethyl 4-(4-nitrobenzoyl)isoxazole-3,5-dicarboxylate (**4da**).* White solid; mp 94–95 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.36 (d, *J*=8.8 Hz, 2H), 8.04 (d, *J*=8.8 Hz, 2H), 4.38–4.30 (m, 4H), 1.27 (t, *J*=7.2 Hz, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 184.8, 158.9, 157.7, 154.9, 154.8, 150.8, 140.2, 130.1, 124.0, 122.6, 63.4, 63.2, 13.8, 13.6; IR (KBr): 1759, 1733, 1691, 1529, 1269, 1227, 1027, 850 cm^{-1}; HRMS (ESI): *m/z* $[M+NH_4]^+$ calcd for $C_{16}H_{18}N_3O_8$: 380.1088; found: 380.1094.

*4.4.5. Diethyl 4-(1-naphthoyl)isoxazole-3,5-dicarboxylate (**4ea**).* - White solid; mp 94–96 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 9.18 (d, *J*=7.8 Hz, 1H), 8.09 (d, *J*=7.8 Hz, 1H), 7.93 (d, *J*=7.8 Hz, 1H), 7.74–7.60 (m, 3H), 7.45 (t, *J*=7.8 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 1.11 (t, *J*=7.2 Hz, 3H), 0.96 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 187.4, 158.4, 157.9, 155.2, 155.0, 135.1, 133.8, 133.0, 132.5, 130.7, 129.1, 128.5, 126.9, 125.9, 124.9, 124.1, 62.8, 13.6, 13.4; IR (KBr): 1678, 1659, 1596, 1579, 1300, 1243, 906 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}NO_6$: 368.1129; found: 368.1132.

*4.4.6. Diethyl 4-(2-naphthoyl)isoxazole-3,5-dicarboxylate (**4fa**).* - White solid; mp 102–103 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.17 (s, 1H), 8.03 (d, *J*=8.4 Hz, 1H), 7.95 (d, *J*=8.4 Hz, 1H), 7.91–7.89 (m, 2H), 7.64 (t, *J*=7.2 Hz, 1H), 7.56 (t, *J*=7.2 Hz, 1H), 4.31–4.23 (m, 4H), 1.17 (t, *J*=7.2 Hz, 3H), 1.08 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 186.1, 158.6, 157.9, 155.2, 155.1, 136.1, 133.6, 132.3, 132.23, 132.17, 129.7, 129.2, 128.9, 127.9, 127.1, 123.6, 63.0, 62.9, 13.6, 13.5; IR (KBr): 1756, 1678, 1223, 1189, 1026 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}NO_6$: 368.1129; found: 368.1124.

*4.4.7. Diethyl 4-(4-chlorobenzoyl)isoxazole-3,5-dicarboxylate (**4ga**).* White solid; mp 81–82 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.77 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=8.4 Hz, 2H), 4.34–4.29 (m, 4H), 1.24 (t, *J*=7.2 Hz, 3H), 1.17 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 185.0, 158.6, 157.9, 155.1, 155.0, 141.0, 134.5, 130.5, 129.3, 123.1, 63.2, 63.1, 13.7, 13.6; IR (KBr): 1751, 1689, 1595, 1311, 1271, 1181, 913 cm^{-1}; HRMS (ESI): *m/z* $[M+NH_4]^+$ calcd for $C_{16}H_{19}ClN_2O_6$: 352.0582; found: 352.0579.

*4.4.8. Diethyl 4-(4-bromobenzoyl)isoxazole-3,5-dicarboxylate (**4ha**).* White solid; mp 110–111 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.69 (d, *J*=8.4 Hz, 2H), 7.65 (d, *J*=8.4 Hz, 2H), 4.35–4.28 (m, 4H), 1.24 (t, *J*=7.2 Hz, 3H), 1.17 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 185.3, 158.6, 157.8, 155.1, 154.9, 134.9, 132.2, 130.6, 129.9, 123.1, 63.2, 63.1, 13.7, 13.6; IR (KBr): 1749, 1689, 1588, 1310, 1270, 1227, 1182, 912, 862 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}BrNO_6$: 396.0077; found: 396.0083.

*4.4.9. Diethyl 4-(4-fluorobenzoyl)isoxazole-3,5-dicarboxylate (**4ia**).* White solid; mp 67–69 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.88–7.85 (m, 2H), 7.18 (t, *J*=8.4 Hz, 2H), 4.36–4.28 (m, 4H), 1.24 (t, *J*=7.2 Hz, 3H), 1.16 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 184.7, 167.3, 165.6, 158.5, 157.9, 155.1, 154.9, 132.7, 132.0, 131.9, 123.2, 116.3, 116.1, 63.1, 63.0, 13.7, 13.6; ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 184.7, 166.4 (d, J^{19}_{C-F}=255.8 Hz), 158.5, 157.9, 155.1, 154.9, 132.7, 132.0, 131.9 (d, J^{19}_{C-F}=10.4 Hz), 123.2, 116.2 (d, J^{19}_{C-F}=22.7 Hz), 63.1, 63.0, 13.7, 13.6; IR (KBr): 1738, 1680, 1598, 1272, 1227, 1027, 916, 850 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}FNO_6$: 336.0878; found: 336.0882.

*4.4.10. Diethyl 4-(thiophene-2-carbonyl)isoxazole-3,5-dicarboxylate (**4ja**).* White solid; mp 78–79 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.79–7.78 (m, 1H), 7.44–7.43 (m, 1H), 7.15–7.14 (m, 1H), 4.37–4.30 (m, 4H), 1.25 (t, *J*=7.2 Hz, 3H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 177.9, 158.7, 157.8, 155.1, 154.7, 143.4, 136.0, 134.9, 128.5, 123.0, 63.1, 63.0, 13.7, 13.6; IR (KBr): cm^{-1}; 1749, 1734, 1653, 1599, 1389, 1290, 1226, 1027, 846, 748; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_6S$: 324.0536; found: 324.0540.

*4.4.11. Diethyl 4-(furan-2-carbonyl)isoxazole-3,5-dicarboxylate (**4ka**).* White solid mp 93–94 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.63 (s, 1H), 7.25 (s, 1H), 6.62 (s, 1H), 4.37–4.34 (m, 4H), 1.28 (t, *J*=7.2 Hz, 3H), 1.23 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 173.1, 159.1, 157.9, 155.2, 154.9, 152.3, 147.8, 122.1, 119.7, 113.1, 63.1, 63.0, 13.7, 13.6; IR (KBr): 1743, 1668, 1565, 1244, 1028 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_7$: 308.0765; found: 308.0763.

*4.4.12. Diethyl 4-(benzofuran-2-carbonyl)isoxazole-3,5-dicarboxylate (**4la**).* White solid; mp 85–86 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.73 (d, *J*=8.0 Hz, 1H), 7.57–7.51 (m, 3H), 7.37–7.35 (m, 1H), 4.36–4.30 (m, 4H), 1.24 (t, *J*=7.2 Hz, 3H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 175.0, 159.3, 157.8, 156.1, 155.1, 154.9, 151.9, 129.2, 126.7, 124.3, 123.6, 122.0, 115.6, 112.4, 63.1, 63.0, 13.6, 13.6; IR (KBr): 1756, 1740, 1672, 1552, 1244, 1024 cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{15}NNaO_7$: 380.0741; found: 380.0739.

*4.4.13. Diethyl 4-cinnamoylisoxazole-3,5-dicarboxylate (**4ma**).*- Yellow solid; mp 108–110 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.55 (d, *J*=7.2 Hz, 2H), 7.44–7.40 (m, 3H), 7.34 (d, *J*=16.2 Hz, 1H), 7.05 (d, *J*=16.2 Hz, 1H), 4.43–4.38 (m, 4H), 1.35 (t, *J*=7.2 Hz, 3H), 1.32 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 185.6, 158.3, 158.1, 155.3, 154.9, 147.4, 133.7, 131.4, 129.1, 128.7, 126.8, 123.6, 63.1, 63.0, 13.9, 13.8; IR (KBr): 1749, 1651, 1618, 1269, 1222, 1184, 1026 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{18}NO_6$: 334.1129; found: 334.1130.

*4.4.14. (E)-Diethyl 4-(3-(4-methoxyphenyl)acryloyl)isoxazole-3,5-dicarboxylate (**4na**).* Yellow solid; mp 143–144 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.49 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=16.0 Hz, 1H), 6.95–6.91 (m, 3H), 4.41–4.38 (m, 4H), 3.85 (s, 3H), 1.37–1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 185.4, 162.4, 158.3, 158.2, 155.4, 155.0, 147.2, 130.6, 126.3, 124.7, 123.9, 114.6, 63.1, 62.9, 55.5, 13.9; IR (KBr): 1743, 1658, 1599, 1511, 1306, 1268, 1224, 1022 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NO_7$: 374.1234; found: 374.1236.

*4.4.15. (E)-Diethyl 4-(3-(4-nitrophenyl)acryloyl)isoxazole-3,5-dicarboxylate (**4oa**).* Yellow solid; mp 148–150 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.27 (d, *J*=8.4 Hz, 2H), 7.71 (d, *J*=8.4 Hz, 2H), 7.42 (d, *J*=16.2 Hz, 1H), 7.15 (d, *J*=16.2 Hz, 1H), 4.45–4.41 (m, 4H), 1.39–1.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 184.9, 158.5, 158.0, 155.2, 154.8, 148.9, 143.4, 139.8, 129.9, 129.2, 124.2, 123.5, 63.3, 63.2, 13.9, 13.8; IR (KBr): 1743, 1660, 1630, 1521, 1346, 1187, 1026 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_8$: 389.0979; found: 389.0975.

*4.4.16. Diethyl 4-((2E,4E)-5-phenylpenta-2,4-dienoyl)isoxazole-3,5-dicarboxylate (**4pa**).* Yellow oil; ^1H NMR ($CDCl_3$, 600 MHz):

δ (ppm) 7.48 (d, *J*=7.2 Hz, 2H), 7.39–7.34 (m, 3H), 7.14–7.10 (m, 1H), 6.97–6.96 (m, 2H), 6.58 (d, *J*=15.0 Hz, 1H), 4.44–4.39 (m, 4H), 1.38–1.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 185.5, 158.2, 158.1, 155.3, 154.9, 147.3, 143.4, 135.5, 129.9, 129.7, 128.9, 127.5, 126.0, 123.7, 63.1, 63.0, 13.9, 13.8; IR (KBr): 1749, 1651, 1618, 1314, 1269, 1222, 1184, 1025 cm^{-1}; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{20}H_{20}NO_6$: 370.1285; found: 370.1279.

4.4.17. 1,1′-(4-Benzoylisoxazole-3,5-diyl)bis(2-methylpropan-1-one) (***4ab***). White solid; mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.77 (d, *J*=7.8 Hz, 2H), 7.59 (t, *J*=7.8 Hz, 1H), 7.45 (t, *J*=7.8 Hz, 2H), 3.58 (hept, *J*=6.6 Hz, 1H), 3.41 (hept, *J*=6.6 Hz, 1H), 1.24–1.22 (m, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 196.5, 192.3, 187.0, 163.7, 159.5, 136.0, 134.1, 128.9, 128.8, 122.2, 38.4, 38.1, 18.0, 17.5; IR (KBr): 1707, 1675, 941, 906 cm^{-1}; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{18}H_{19}NNaO_4$: 336.1206; found: 336.1201.

4.4.18. Isoxazole-3,4,5-triyltris(phenylmethanone) (***4ac***). White solid; mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.28 (d, *J*=7.6 Hz, 2H), 8.13 (d, *J*=7.6 Hz, 2H), 7.85 (d, *J*=7.2 Hz, 2H), 7.71–7.52 (m, 7H), 7.44 (t, *J*=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 187.1, 183.6, 180.2, 164.9, 160.6, 136.4, 134.85, 134.80, 134.7, 134.4, 134.0, 130.8, 130.2, 129.1, 128.9, 128.8, 125.4, 109.7; IR (KBr): 1726, 1675, 1658, 1597, 1581, 1257, 1233, 906, 684 cm^{-1}; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{24}H_{15}NNaO_4$: 404.0893; found: 404.0885.

4.4.19. (4-Benzoylisoxazole-3,5-diyl)bis(p-tolylmethanone) (***4ad***). White solid; mp 150–152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.18 (d, *J*=7.8 Hz, 2H), 8.04 (d, *J*=7.8 Hz, 2H), 7.84 (d, *J*=7.2 Hz, 2H), 7.56 (t, *J*=7.2 Hz, 1H), 7.42 (t, *J*=7.8 Hz, 2H), 7.33–7.32 (m, 4H), 2.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 187.1, 183.1, 179.8, 165.2, 160.7, 146.2, 146.0, 136.5, 133.8, 132.3, 132.0, 130.8, 130.7, 130.3, 129.6, 129.5, 129.0, 128.7, 125.1, 21.9; IR (KBr): 1659, 1603, 1263, 1182, 904 cm^{-1}; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{26}H_{20}NO_4$: 410.1387; found: 410.1396.

4.4.20. (4-Benzoylisoxazole-3,5-diyl)bis((4-methoxyphenyl)-methanone) (***4ae***). White solid; mp 156–157 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.16 (d, *J*=7.8 Hz, 2H), 8.01 (d, *J*=7.8 Hz, 2H), 7.84 (d, *J*=7.8 Hz, 2H), 7.60 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.2 Hz, 2H), 7.01–7.00 (m, 4H), 3.92 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 187.4, 181.9, 178.5, 165.4, 165.0, 164.9, 160.9, 136.6, 133.8, 133.3, 132.8, 129.1, 128.7, 127.9, 127.5, 124.9, 114.3, 114.1, 55.64, 55.60; IR (KBr): 1682, 1656, 1594, 1325, 1258, 1169, 905 cm^{-1}; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{26}H_{19}NNaO_6$: 464.1105; found: 464.1129.

4.4.21. (4-Benzoylisoxazole-3,5-diyl)bis((4-nitrophenyl)methanone) (***4af***). White solid; mp 151–152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.49 (d, *J*=7.8 Hz, 2H), 8.40–8.39 (m, 4H), 8.33 (d, *J*=7.8 Hz, 2H), 7.86 (d, *J*=7.8 Hz, 2H), 7.65 (t, *J*=7.8 Hz, 1H), 7.50 (t, *J*=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 186.2, 181.9, 178.4, 163.9, 160.1, 151.11, 151.06, 138.8, 138.6, 135.9, 134.6, 131.8, 131.2, 129.03, 128.99, 126.4, 124.1, 123.9; IR (KBr): 1676, 1600, 1527, 1351, 1253, 908, 887 cm^{-1}; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{24}H_{13}N_3NaO_8$: 494.0595; found: 494.0580.

4.4.22. (4-Benzoylisoxazole-3,5-diyl)bis((4-chlorophenyl)methanone) (***4ag***). White solid; mp 145–147 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.24 (d, *J*=8.4 Hz, 2H), 8.08 (d, *J*=8.4 Hz, 2H), 7.84 (d, *J*=7.2 Hz, 2H), 7.58 (t, *J*=7.2 Hz, 1H), 7.51–7.49 (m, 4H), 7.44 (t, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 186.8, 182.1, 178.7, 164.6, 160.4, 141.7, 141.6, 136.2, 134.1, 132.9, 132.6, 132.1, 131.5, 129.4, 129.2, 129.0, 128.8, 125.7; IR (KBr): 1727, 1680, 1661, 1587, 1258, 1236, 1092, 904 cm^{-1}; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{24}H_{14}Cl_2NO_4$: 450.0294; found: 450.0308.

4.4.23. (4-Benzoylisoxazole-3,5-diyl)bis((4-bromophenyl)methanone) (***4ah***). White solid; mp 167–169 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.16 (d, *J*=8.4 Hz, 2H), 8.01 (d, *J*=8.4 Hz, 2H), 7.84 (d, *J*=7.2 Hz, 2H), 7.69–7.68 (m, 4H), 7.60 (t, *J*=7.2 Hz, 1H), 7.45 (t, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 186.8, 182.4, 179.0, 164.6, 160.4, 136.2, 134.2, 133.3, 133.0, 132.4, 132.2, 132.1, 132.0, 131.5, 130.6, 129.0, 128.8, 125.7; IR (KBr): 1725, 1683, 1658, 1304, 1256, 1236, 903, 881 cm^{-1}; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{24}H_{14}Br_2NO_4$: 539.9274; found: 539.9294.

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Supplementary data

The general experimental methods and the characterizing data including ^{1}H NMR, ^{13}C NMR, IR, and HRMS for compound **4** are available in Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.055.

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14. CCDC 861459–861460 (**4aa**, **4ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.
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